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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/095,536	06/10/1998	JOHN A. KINK	OPHD-03282	9749

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EXAMINER	
HISSONG, BRUCE D	
ART UNIT	**PAPER NUMBER**
1646	

MAIL DATE	DELIVERY MODE
08/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/095,536	KINK, JOHN A.	
	Examiner	Art Unit	
	Bruce D. Hissong, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133) Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. The Applicant's response to the office action mailed on 3/19/2007, including arguments/remarks and amended claims, was received on 6/22/2007 and has been entered into the record.

2. Claims 49-57 are currently pending and are the subject of this office action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 49-57 *remain rejected* under 35 USC § 103(a) as being obvious in view of the combination of Skurkovich *et al* ("Skurkovich"), Starnes *et al* ("Starnes"), and Doherty *et al* ("Doherty"), as set forth on pages 2-4 of the office action mailed on 3/19/2007.

The claims of the instant invention are drawn to a method of treating a mammal having a plurality of symptoms of sepsis, or a mammal having sepsis, or a mammal having septic shock, wherein said method comprises administering to said mammal a therapeutic composition comprising anti-TNF, anti-IL-6, and anti-IFN antibodies, and wherein said sepsis, symptoms of sepsis, or septic shock is reduced.

Skurkovich teaches a composition comprised of anti-TNF, anti-IL-6, and anti-IFN antibodies, but does not specifically teach administration of this composition for the treatment of a mammal having symptoms of sepsis, a mammal having sepsis, or a mammal having septic shock.

Starnes demonstrates a role for both IL-6 and TNF-α in mediating the pathogenesis of sepsis and septic shock (see abstract, p. 4185, 2nd column). Starnes also teaches that administration of neutralizing anti-TNF-α antibodies prevents mortality associated with septic

shock (see Figure 4), and also inhibits IL-6 expression after E. coli exposure (p. 4185, last paragraph). Furthermore, Starnes discloses that administration of anti-IL-6 antibodies also protects against a lethal exposure to E. coli (see Figure 4).

Doherty demonstrates a role for both TNF-α and IFN-γ in mediating the pathogenesis of sepsis and septic shock, and also teaches that administration of either anti-TNF-α or anti-IFN-γ neutralizing antibodies protects against endotoxin lethality (see abstract, Figure 3).

In the response received on 6/22/2007, the Applicant argues that the combination of Skurkovich, Starnes, and Doherty does not render the instant claims obvious because Skurkovich does not teach treatment of a mammal having a plurality of symptoms of sepsis, and does not specifically teach treatment of a mammal exhibiting hypotension. Furthermore, the Applicant argues that the specification of the instant invention shows administration of anti-IFN-γ antibodies alone, as well as administration of anti-IFN-γ and anti-TNF-α antibodies in combination, failed to save any test animals challenged with a lethal dose of LPS (see Table 3). However, Table 5 shows that combined administration of anti-IFN-γ, anti-TNF-α, and anti-IL-6 antibodies protected mice from a lethal LPS challenge. Because of the failure of anti-IFN-γ antibodies alone, or the combination of anti-IFN-γ and anti-TNF-α antibodies to protect lethally challenged mice, the Applicants argue that the results of Table 5 regarding the combination of all three antibodies represents unexpectedly improved results. Therefore, the assertion of obviousness is overcome by this demonstrated improved performance over the prior art.

These arguments have been fully considered and are not persuasive. With regards to the Applicants argument that the claims are not obvious because Skurkovich does not teach treatment of a mammal having a plurality of symptoms of sepsis, it is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the claims are obvious over the combination of Skurkovich, which teaches a composition comprising anti-IFN-γ, anti-TNF-α, and anti-IL-6 antibodies, and Starnes and Doherty, which collectively disclose important roles for IFN-γ, TNF-α, and IL-6 in mediating the pathogenesis of sepsis, as well as treatment of sepsis with anti-IFN-γ, anti-TNF-α, and anti-IL-6 antibodies individually. Even if Starnes and Doherty did not disclose anti-IFN-γ, anti-TNF-α, and anti-IL-6 treatment of sepsis, they would motivate a skilled artisan to neutralize or inhibit the activity of all three cytokines because the references teach important roles for all three cytokines in mediating or

promoting the pathogenesis of sepsis. Thus, the disclosures of Starnes and Doherty would provide one of ordinary skill in the art with the motivation to administer the composition taught by Skurkovich.

In response to Applicant's arguments that the specification demonstrates unexpectedly improved results, it is noted Table 3 shows administration of anti-IFN-γ or combined anti-IFN-γ and anti-TNF-α 60 minutes post-challenge, while Table 5 shows administration of combined anti-IFN-γ, anti-TNF-α, and anti-IL-6 antibodies 5 minutes post-challenge. One of skill in the art would not know whether the results presented in Table 5 are truly unexpected, or are merely differences due to the timing of antibody administration after LPS challenge. Would administration of anti-IFN-γ, or combined anti-IFN-γ and anti-TNF-α antibodies at 5 minutes post-challenge offer the same degree of protection as the combination of all three antibodies at 5 minutes post challenge? For these reasons and those set forth *supra*, the specification fails to convincingly demonstrate unexpected results, and therefore the claims are obvious in view of the combination of Skurkovich, Starnes, and Doherty.

Conclusion

No claim is allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571) 272-3324.

The examiner can normally be reached M-F from 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D., can be reached at (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BDH
Art Unit 1646

/Robert S. Landsman/
Primary Examiner, Art Unit 1647